Safety of Targeted Therapy and its Impact on the Compliance of Oncology Patients

Fadi Farhat, MD, MHHM
1. **Compliance/Adherence to treatment in oncology patients**
2. Emerging Trends in Cancer Care
3. Non-adherence to antineoplastic drugs
4. Antineoplastic treatment: The special case of targeted agents?
5. Strategies To Improve Adherence
6. Conclusion
Defining Adherence and Recognizing Its Prevalence

- In 2003, a World Health Organization multidisciplinary group determined the term *compliance* to be too closely associated with blame.
- **Adherence** was defined as “the extent to which a person’s behavior—taking medications, or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.”
- A patient is considered to be non-adherent if he or she misses doses, takes additional or wrong doses, as opposed to what is prescribed, or takes doses at the wrong time (Ruddy, Mayer, & Partridge, 2009).
Defining Adherence and Recognizing Its Prevalence

• WHO projects that approximately 50% of patients typically take their medicines as prescribed.

• This percentage varies based on type of medication and disease:
  – Patients with HIV, arthritis, GI disorders, and cancer have a higher incidence of adherence
  – diabetes and sleep disorders - lower rate of adherence to medications

• Adherence issues are not new—primary care providers (PCPs) have acknowledged that there is a high prevalence of nonadherence to treatment regimens for chronic diseases such as diabetes and heart failure.
Adherence in Oncological patients

• In oncology, a higher level of adherence is expected, since cancer is generally perceived as a life-threatening and serious disease by patients.
  – (Lebovits et al., 1990; Partridge, Avorn, Wang, & Winer, 2002; Thompson, Dewar, Fahey, & McCowan, 2007).

• Adherence to prescribed cancer therapy is more than just taking your medicine on time—nonadherence can result in drug resistance, low response to therapy, disease progression, and death.
The report suggests that “increasing the effectiveness of adherence interventions may have a far greater impact on the health of the population than any improvement in specific medical treatment”

Drugs Don’t Work In Patients Who Don’t Take Them !
Agenda

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a) - Increasing use of oral therapies

- The use of oral cancer therapies for the treatment of cancer has experienced a rapid increase in recent years and this is expected to continue.
- An estimated 25% of anticancer therapies in the research pipeline have been designed for oral administration (Michaud & Choi, 2008).
- Putting the ownness on the patient and caregiver to manage their cancer treatment, brings the issue of patient nonadherence and its' detrimental effect on patient outcomes, to the limelight.
- Oral therapies also change the site of care, from the cancer center infusion suite to the patient's home.
b)- Molecularly targeted therapies with attenuated side effects vs. traditional chemotherapy and permanent administration

- The use of targeted oral anticancer medications (OAMs) is becoming increasingly prevalent in cancer care.
- Approximately 25-30% of the oncology drug pipeline involves oral agents and there are now over 50 OAMs approved by the FDA.
- This change represents a major shift in management of patients with cancer from directly observed, intermittent intravenous therapy to self-administered, oral chronic therapy.
- The increased prevalence of OAMs raises the issue of adherence in oncology, including understanding the challenges of adherence to OAMs.
c) - Considering cancer a chronic disease with new emphasis on ongoing therapy

• Cancer patients who experience significant disease-related symptoms, similar to patients with active asthmatic conditions, are more likely to adhere to treatment and be motivated to achieve consistent levels of control.

• However, disease progression or symptoms of cancer may not be evident during oral therapy with targeted agents.

• In turn, medication adherence may diminish in a manner similar to that seen with antihypertensive medications, where the evidence of effect is often not readily perceived.
d) - Longer survival times requiring long-term daily medication - The Example Of Imatinib

- **Success** rates with imatinib are high, but to achieve—and maintain—these results, **long-term administration** is required in responsive patients.

- Dosing protocols may include holidays and step-downs to control side effects and neutropenia.
  - These interruptions can lead patients to believe that poor adherence is routine and acceptable,
  - When in fact resistant clones have been found to develop with poor imatinib adherence.

- There is also a risk of rapid relapse when patients discontinue imatinib therapy, even in those with CML in complete remission with no detectable evidence of disease {%}
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Non-adherence to antineoplastic drugs

• The convenience associated with the self-administration of oral therapy, the requirement of fewer trips to the physician's office, and the lack of infusion reactions are all benefits for patients, allowing them to potentially maintain their relative independence while undergoing active anticancer treatment.

• On the other hand, there are growing concerns regarding patients' poor adherence to oral therapy as well as the challenges of monitoring patient compliance when treatment administration does not occur in the presence of health care professional (HCPs).
Consequences of suboptimal or non-adherence

- Consequences of to proven cancer therapy may detrimentally affect the patients' clinical outcomes:
  - development of treatment resistance, progressive disease, and death.
- **Suboptimal adherence** may be the biggest barrier to the use of newer oral antineoplastics and the long-term success of these therapies.
- Some oral antineoplastics, patients may be prone to self-modulating their doses because of actual or potential toxicity leading the practitioner to modify the dose or change to an alternative agent because of apparent nonresponse.
The case of oral chemotherapy

• The few published studies on adherence to oral chemotherapy show the extent of the problem.
• Adherence to an oral cyclophosphamide regimen was only 57% in one study of breast cancer patients.
• Another study of 108 patients with hematologic malignancies showed adherence rates of 27% for prednisone and 17% for allopurinol.
• In a small study of 50 adolescent and young adults with Hodgkin’s disease and acute lymphoblastic leukemia, 52% were nonadherent to treatment with prednisone.
The case of Tamoxifen in Breast Cancer

• In a study of 2,378 patients who began adjuvant tamoxifen therapy for primary breast cancer between 1990 and 1996, adherence during the first year of treatment was 87%, but declined to only 50% after 4 years.

• The investigators concluded that nearly one fourth of tamoxifen-treated patients may be at risk for suboptimal clinical response because of poor adherence.

• Another study used a convenience sample of 597 women with early-stage breast cancer and found that 17% of those prescribed tamoxifen discontinued it within the first 2 years, and 68% of these women took it for less than 1 year.
Evaluate the compliance rate in France for such therapies

• **Primary Objective** - compliance assessed based on Medication Possession Ratio (MPR): number of doses taken divided by number of doses expected.

• **Population**: patients >18 years, OCT and/or OTT, able to manage oral treatment alone and to swallow.

• **Chemotherapies** 128 (85%): capecitabine 96 (64%), vinorelbine 12 (8%) cyclophosphamide 11 (7.3%), others 9 (6%)

• **Targeted therapies** 22 (15%): sunitinib 8 (5.3%), everolimus 6 (4%), gefitinib 3 (2%), lapatinib 2 (1.3%), imatinib 2 (1.3%), sorafenib 1 (0.6%).

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Results & Conclusions of the Prospective study

• 90.3% - considered themselves as autonomous,
  – Important compliance of 91%,
• 89.4% - well informed about toxicities
• 95.6% - didn’t stop treatment in case of major toxicity
  – Also the risk of over-treatment.
• So the question in oral cancer treatment would be not
  “is the treatment taken?” But
  “is the treatment stopped before major toxicity?”
• That would be the main goal of a patient education program.

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Erlotinib
Gefitinib
Bevacizumab
Sunitinib
Sorafenib
Chemotherapy
Panitumumab
Cetuximab
Temsirolimus

Inhibition of programmed cell death (apoptosis)
Tumor cell proliferation
Tumor cell invasion
Development of tumor vasculature (angiogenesis)
Side effects of targeted therapy drugs

• Although targeted therapy drugs don’t affect the body the same way that standard chemo drugs do, they still cause SEs.

• Side effects from these drugs depend largely on what the drug targets. Some drugs target substances that are more common on cancer cells, but are also found on healthy cells:
  – So these drugs may affect healthy cells, too, causing some side effects.

• When drugs attack more than one target, SEs are more likely.

• Drugs that act as angiogenesis inhibitors affect new blood vessel formation all over the body, not just those near the ca:
  – This can lead to side effects, as well.
# Sever Side Effects of Targeted Therapies

<table>
<thead>
<tr>
<th>Severe side-effects of Anti-Angiogenic Treatment</th>
<th>Incidence Grade 3/4</th>
<th>Severe side-effects of anti-EGFR</th>
<th>Incidence Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>11-16%</td>
<td>Skin Reactions</td>
<td>15%</td>
</tr>
<tr>
<td>Hypersensitivity / Infusion Reactions</td>
<td>0.4%*</td>
<td>• Mucositis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Dry skin</td>
<td></td>
</tr>
<tr>
<td>Arterial Thromboembolic Events</td>
<td>3.3-10% (0.8% fatal)</td>
<td>• Increased tiredness</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Mucositis/stomatitis</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal Perforation</td>
<td>1.4-2% (0.4-1% fatal)</td>
<td>• Fissure of the skin</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>• Xerostomia</td>
<td></td>
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<tr>
<td>Wound Heeling /Bleeding Complications in Surgical Patients</td>
<td>10-20%</td>
<td>• Dysphagia</td>
<td></td>
</tr>
<tr>
<td>Haemorrhage (overall)</td>
<td>4%</td>
<td>Hypersensitivity / Infusion Reactions</td>
<td>2.5%</td>
</tr>
<tr>
<td>-Tumor-Associated CRC</td>
<td>1-3%</td>
<td></td>
<td></td>
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<tr>
<td>-Epistaxis in CRC patients</td>
<td>22-34.3%</td>
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Cutaneous manifestations of anti-angiogenic therapy in oncology: Review with focus on VEGF inhibitors

Rim S. Ishak a, Simon Abi Aad b, Angela Kyei a, Fadi S. Farhat c, d, e, f

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d Lebanese University, Beirut, Lebanon
e Saint Joseph University, Beirut, Lebanon

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Erythematous reaction produced by treatment, hypothesized to be the result of an inflammatory reaction typical of the treatment,

3.2.1.4. The authors implicated the following drugs: sunitinib, sorafenib, and anti-VEGFR inhibitors, with an dermatological phenotype of acneiform to papulosquamous eruptions seen in patients treated with these agents. The pathogenesis is characterized by increased expression of PDGFR receptors, leading to increased reactive oxygen species (ROS).

3.2.1.3. It has been observed that patients with lessened immune reactivity due to treatment may develop a more severe reaction, which is thought to be the result of a blockage of other receptors.

Fig. 2. A typical erythematous reaction produced by treatment, illustrating the inflammatory nature of the reaction, which is characterized by increased expression of PDGFR receptors, leading to increased reactive oxygen species (ROS).

Fig. 3. A typical erythematous reaction produced by treatment, illustrating the inflammatory nature of the reaction, which is characterized by increased expression of PDGFR receptors, leading to increased reactive oxygen species (ROS).
Hypertension induced by chemotherapeutic and immunosuppressive agents: A new challenge

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Strategies and Reinforcers To Improve Adherence With Oral Agents

### Multidisciplinary Approach

<table>
<thead>
<tr>
<th>All members of the healthcare team should be made aware of adherence issues and barriers, and reinforce to patients the importance of medication adherence</th>
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<tbody>
<tr>
<td>Nurses play an especially important role in educating patients about their medications</td>
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### Follow-up

<table>
<thead>
<tr>
<th>Monitor adherence and persistence regularly Restrict refills as appropriate</th>
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<tbody>
<tr>
<td>Contact patients who miss appointments</td>
</tr>
<tr>
<td>Provide ongoing counseling and education</td>
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</table>
Strategies and Reinforcers To Improve Adherence With Oral Agents - 2,6,7,24

**Educational**

- Identify patients at high risk for poor adherence and target them for personalized interventions
- Provide education on drug’s actions, expectations of positive and negative effects, and how to manage side effects
- Explain the purpose of drug holidays and step-downs, and the importance of patients not altering therapy on their own
- Individualize interventions according to patient needs
- Encourage self-monitoring of test results
- Encourage the development of a home dosing routine
- Encourage the use of pillboxes, medication diaries, and other adherence aids
- Provide coaching on pill taking and supervised practice time using adherence aids
Strategies and Reinforcers To Improve Adherence With Oral Agents - 2,6,7,24

<table>
<thead>
<tr>
<th>Organizational</th>
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<tbody>
<tr>
<td>Define and explain therapeutic success measures</td>
</tr>
<tr>
<td>• Success in disease control increases patient satisfaction and reinforces adherence</td>
</tr>
<tr>
<td>Make each visit as convenient and efficient as possible</td>
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<tr>
<td>Maintain open communication with patients and caregivers</td>
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<tr>
<td>• Be sure they know whom to call when questions arise</td>
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<tr>
<td>• Foster an environment of trust and psychological support</td>
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<table>
<thead>
<tr>
<th>Social</th>
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<tbody>
<tr>
<td>Provide consistent support to increase patients’ belief in the healthcare process and its worth</td>
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<tr>
<td>• Provide options for economic assistance when needed</td>
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<tr>
<td>• Assess and encourage home psychological support</td>
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In Summary

• Adherence issues are not new - there is a high prevalence of non-adherence to treatment regimens for chronic diseases

• Increasing the effectiveness of adherence interventions may have a greater impact on the health of the population than any improvement in specific medical treatment
In Summary

- Emerging Trends in Cancer Care: Increasing use of oral therapies, use of targeted oral anticancer medications in cancer care, Long term daily medication required in responsive patients...

- Poor adherence to proven therapies may detrimentally affect the patients' clinical outcomes, such as survival
In Summary

- Urgent need to identify more effective strategies to measure and monitor adherence to anticancer agents - to maximize therapeutic benefits
Back up Slides
## Barriers to Optimal Adherence

<table>
<thead>
<tr>
<th>Patient Deficits</th>
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<tbody>
<tr>
<td>Physical factors</td>
</tr>
<tr>
<td>Knowledge Deficit</td>
</tr>
<tr>
<td>Attitude, confidence, motivation</td>
</tr>
<tr>
<td>Psychological/behavioral/developmental factors</td>
</tr>
<tr>
<td><strong>Perceived benefit of treatment</strong></td>
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<tr>
<td>Fear of possible adverse effects</td>
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<tr>
<td>Stress/anxiety/anger</td>
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<tr>
<td>Alcohol or substance abuse</td>
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</tbody>
</table>
## Barriers to Optimal Adherence

<table>
<thead>
<tr>
<th>Social Barriers</th>
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<tbody>
<tr>
<td>Low language literacy</td>
</tr>
<tr>
<td>Lack of family or social support</td>
</tr>
<tr>
<td>Homelessness</td>
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<tr>
<td>Lack of health insurance/medication cost/copays</td>
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<tr>
<td>Limited access to a pharmacy</td>
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<tr>
<td>Busy work or social lifestyle</td>
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</table>
## Barriers to Optimal Adherence

### Treatment Regimen
- Complex regimen
- Lack of quick benefit
- Side effects
- Requires significant behavioral changes

### Healthcare System
- Poor provider communication skills
- Poor patient-provider relationship
- Lack of knowledge on adherence
- Lack of reinforcement from healthcare provider
- Patient information materials written at a high literacy level
Molecular Targets?

Input layer

Signal-processing layer

Output layer

LPA, thrombin
TGfα
Epiregulin
b-cellulin
HB-EGF
Amphiregulin
NRG1
NRG2
NRG3
NRG4
Cytokines

Ligands

Receptor dimers
Adaptors & enzymes
Cascades
Transcription factors

Src
Cbl
PLCγ
PI3K
Shp2
GAP
Ras-GTP
Ras-GDP
Sos
Grb2
Nck
Ras
MAPK
MEK
RAF
JNK
JNKK
PAK
Abl
Rac
Vav
Crk
Jak

Elk
Jun
Fos
Myc
Sp1
Egr1
Stat

Apoptosis
Migration
Growth
Adhesion
Differentiation
Types of targeted therapy used today

Today many different types of targeted therapies are used to treat cancer. Looking at examples helps a person understand how these drugs work. There are many different targeted therapies in use and new ones are coming out all the time. There are 2 main types of targeted therapy drugs:

- **Antibody drugs** are man-made versions of immune system proteins (called antibodies) that have been designed to attack certain targets on cancer cells. (The body normally makes antibodies to fight harmful invaders like germs.)

- **Small-molecule drugs** are not antibodies. Since antibodies are large molecules, this other type of drug is called a “small-molecule” targeted therapy drug.
e) - Changing needs for patients and caregivers to monitor/manage side effects

- Encouraging test results may also cause patients to believe there is less need for strict treatment adherence.

- Healthcare professionals must regularly reinforce to patients the importance of treatment adherence; even though their condition is improving and symptoms are no longer a reminder of the disease, the disease still lingers.